Crystal and Molecular Structure of Imidazole-4-acetic Acid Hydrochloride

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Crystals of the title compound are orthorhombic, space group $P2_12_12_1$, with a = 20.292(5), b = 4.552(2), c = 7.755(2) Å, Z = 4. The structure was solved by direct methods and refined by least-squares procedures to R 0.041 for 1 060 observed diffraction maxima. The five-membered ring is planar, and molecules are linked by a three-dimensional hydrogen-bond network.

IMIDAZOLE-4-ACETIC ACID (I), a structural analogue of 4-aminobutanoic acid [(II), GABA], has been shown to mimic the inhibitory action of (II) at the crayfish stretch-receptor neurone,[1] and at mammalian cortical neurones,[2] where, it has been suggested, it acts at the GABA receptor.[3,4]

EXPERIMENTAL

Crystals of (I) were grown from a supersaturated aqueous acetone by slow evaporation of solvent. A colourless transparent mass was obtained which was trimmed to give a rectangular prism elongated along the b axis.

TABLE 1

Fractional co-ordinates and thermal motion parameters ($\times 10^4$) * derived from least-squares refinement, with estimated standard deviations in parentheses

Atom	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Cl(1)	3 177(1)	4 820(2)	3 703(1)	307(1)	533(5)	402(3)	148(2)	−4(1)	26(3)
N(3)	1 201(1)	1 732(9)	2 549(4)	269(3)	384(18)	326(9)	66(6)	−46(4)	41(11)
C(2)	1 698(2)	38(12)	2 087(5)	324(3)	530(23)	407(10)	50(8)	25(5)	−60(16)
N(1)	1 939(1)	−1 204(8)	3 494(5)	219(3)	330(15)	556(12)	40(6)	−38(5)	14(12)
C(5)	1 592(2)	−227(11)	4 905(5)	270(3)	532(23)	416(10)	−51(8)	−72(5)	100(17)
C(4)	1 120(1)	1 619(9)	4 312(5)	229(3)	327(17)	372(9)	−47(6)	−20(4)	−30(11)
C(6)	599(2)	3 254(10)	5 239(6)	247(3)	440(20)	571(13)	−79(7)	40(5)	−181(16)
C(7)	−74(2)	1 877(8)	5 113(5)	264(3)	347(16)	351(9)	35(6)	−12(4)	17(12)
O(1)	−502(1)	3 095(7)	6 165(4)	300(2)	550(16)	594(10)	−64(6)	75(4)	−149(13)
O(2)	−203(1)	−104(8)	4 124(4)	331(2)	682(20)	588(10)	−152(6)	42(4)	−267(15)

* The Debye–Waller factor is defined as $T = \exp[-2\pi^2\sum_i\sum_j a_i{}^*a_j{}^*h_ih_jU_{ij}]$ with U in Å².

Crystal Data.—$C_5H_7ClN_2O_2$, M = 162.6. Orthorhombic, a = 20.292(5), b = 4.553(2), c = 7.755(2) Å, U = 716.4 Å³, D_m = 1.51(1), Z = 4, D_c = 1.507 g cm⁻³. Space group $P2_12_12_1$ (No. 19, D_2^4). Mo-K_α radiation, λ = 0.7107 Å; μ(Mo-K_α) = 4.9 cm⁻¹.

Intensity Measurements.—Three-dimensional X-ray diffraction data from a small single crystal (*ca.* 0.32 × 0.63 × 0.30 mm) were collected on a computer-controlled four-circle diffractometer[5] by use of graphite monochromated Mo-K_α radiation. A coupled θ—2θ step scan with $\Delta 2\theta$ 0.04°, a counting time of 5 s per step, and a peak width of 1.6° were used. In the range 2θ 5—60°, 1 060 diffraction maxima of a possible 1 278 in an octant of reciprocal space (h,k,l) had $I \geqslant 3\sigma$ (I) and were considered observed. Data were corrected for Lorentz and polarisation effects but not for absorption or extinction.

Structure Solution and Refinement.—Normalised structure factors $|E|$ were calculated from the observed structure factors in the region 2θ 5—45° by use of the K-curve method, normalising all parity groups of h,k,l separately to obtain the condition $\langle|E|^2\rangle_{av} = 1.0$. An initial set of phases for 139 reflections with $|E| \geqslant 1.2$ was obtained by use of MULTAN.[6] An E map calculated with the phases derived from the most consistent solution revealed the position of the chloride ion and seven other atoms, three of which were related to other peaks by a false mirror plane at $y = 0$. A Fourier synthesis phased with the chloride ion and four atoms which were thought to be part of the imidazole ring produced a satisfactory partial trial-structure and also removed the false symmetry. Further Fourier syntheses enabled location of all non-hydrogen atoms. After successive cycles of full-matrix least-squares refinement a difference electron-density synthesis revealed all hydrogen atom positions. Final cycles of refinement, including hydrogen atom positions by full-matrix least squares were continued until all parameter shifts were $\leqslant 0.1\sigma$. The function minimised was $\Sigma w(|F_o| - |F_c|)^2$ with $w = 4I/\sigma^2$ where $\sigma = \sigma(I) + 0.05I$ (see preceding paper). Atomic scattering factors for neutral

TABLE 2

Fractional co-ordinates for hydrogen atoms ($\times 10^3$), derived from least-squares refinement, with estimated standard deviations in parentheses

Atom	x	y	z
H(3)	95(3)	284(16)	188(8)
H(2)	188(3)	−95(16)	93(8)
H(1)	231(3)	−252(13)	360(8)
H(4)	165(3)	−120(17)	608(8)
H(5)	57(3)	547(16)	514(9)
H(6)	73(3)	328(16)	654(8)
H(7)	−85(3)	215(16)	603(9)

All hydrogen atoms have U_{iso} 0.051 Å².

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carbon, oxygen, and nitrogen, and for the chloride ion were taken from ref. 7 and for hydrogen from ref. 8.

The final R is 0.041 for the 1 060 observed data. Positional and thermal parameters for non-hydrogen atoms are listed in Table 1, hydrogen atom positions in Table 2, bond distances and angles in Tables 3 and 4, and torsion angles in Table 5.

TABLE 3

Interatomic distances (Å) and angles (°) for non-hydrogen atoms, with estimated standard deviations in parentheses

(*a*) Distances			
N(3)–C(2)	1.318(5)	C(4)–C(6)	1.479(5)
C(2)–N(1)	1.323(5)	C(6)–C(7)	1.507(5)
N(1)–C(5)	1.375(5)	C(7)–O(1)	1.313(5)
C(4)–C(5)	1.355(5)	C(7)–O(2)	1.212(5)
C(4)–N(3)	1.378(5)		
(*b*) Angles			
C(4)–N(3)–C(2)	109.8(3)	C(5)–C(4)–C(6)	130.6(4)
N(1)–C(2)–N(3)	108.0(3)	N(3)–C(4)–C(6)	123.3(4)
C(2)–N(1)–C(5)	109.2(3)	C(4)–C(6)–C(7)	114.0(3)
N(1)–C(5)–C(4)	107.0(3)	C(6)–C(7)–O(1)	112.5(3)
C(5)–C(4)–N(3)	106.0(3)	C(6)–C(7)–O(2)	123.1(3)
		O(1)–C(7)–O(2)	124.4(3)

TABLE 4

Interatomic distances (Å) and angles (°) for hydrogen atoms, with estimated standard deviations in parentheses

(*a*) Distances			
H(3)–N(3)	0.88(7)	H(5)–C(6)	1.01(7)
H(2)–C(2)	1.07(7)	H(6)–C(6)	1.04(6)
H(1)–N(1)	0.96(6)	H(7)–O(1)	0.83(7)
H(4)–C(5)	1.02(7)		
(*b*) Angles			
C(4)–N(3)–H(3)	122(4)	C(4)–C(6)–H(5)	120(4)
N(3)–C(2)–H(2)	138(4)	C(4)–C(6)–H(6)	108(4)
C(2)–N(1)–H(1)	129(4)	H(5)–C(6)–H(6)	94(5)
N(1)–C(5)–H(4)	121(4)	C(7)–O(1)–H(7)	105(5)
C(2)–N(3)–H(3)	128(4)	C(5)–N(1)–H(1)	122(4)
N(1)–C(2)–H(2)	113(4)	C(4)–C(5)–H(4)	131(4)

TABLE 5

Torsion angles (°) for non-hydrogen atoms, with estimated standard deviations in parentheses

N(3)–C(2)–N(1)–C(5)	−1.2(5)
C(2)–N(1)–C(5)–C(4)	1.2(5)
N(1)–C(5)–C(4)–N(3)	−0.7(4)
C(5)–C(4)–N(3)–C(2)	0.0(4)
C(4)–N(3)–C(2)–N(1)	0.7(4)
N(1)–C(5)–C(4)–C(6)	178.6(4)
C(5)–C(4)–C(6)–C(7)	−101.6(5)
C(4)–C(6)–C(7)–O(1)	169.7(3)
C(4)–C(6)–C(7)–O(2)	−11.4(6)

Observed and calculated structure factors have been deposited as Supplementary Publication No. SUP 21551 (4 pp.).*

DISCUSSION

The atom numbering scheme is shown in Figure 1, and the molecular packing and hydrogen bonding in Figure 2, viewed in the direction of *b*.

The imidazole ring is planar with H(2) and H(4) being significantly displaced from this plane (Table 6). The geometry of the ring (Figure 3) differs slightly from that in imidazole[9] in that the C(2)–N(1) bond is shorter in (I).

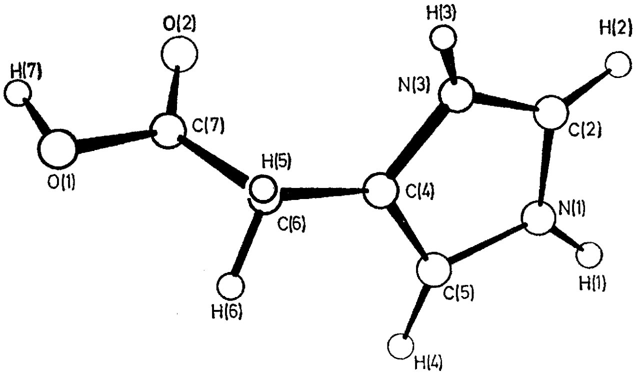

FIGURE 1 Perspective drawing of the molecule illustrating the atom numbering scheme

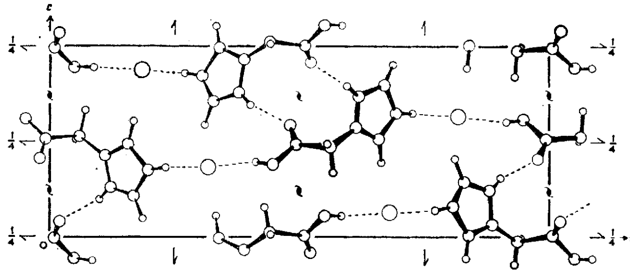

FIGURE 2 Contents of the unit cell viewed in the direction of *b*. Hydrogen bonds are shown as broken lines

TABLE 6

Distances (Å) of relevant atoms from the best mean plane of the imidazole ring and equation of the plane in orthogonal (Å) co-ordinates

Equation: $0.631X + 0.768Y + 0.1057Z = 4.082$

N(3) * −0.002, C(2) * 0.005, N(1) * −0.006, C(5) * 0.005, C(4) * −0.002, C(6) −0.023, H(3) 0.010, H(2) −0.201, H(1) 0.017, H(4) −0.166

* Atoms defining plane.

The ring carries a formal positive charge which would be expected to increase the electron delocalisation in the out-of-plane p orbitals of the sp^2 hybridised ring atoms, thereby increasing the stability of the ring. The shortening of the C(2)–N(1) bond may be thought of as a manifestation of this effect. The sum of the double-bond percentages, as calculated by use of the curve of bond length *vs.* bond order of Pauling[10] for the C–C bond and using an analogous curve constructed by Wheatley[11] for the C–N bonds is 230%. The corresponding value obtained for imidazole[9] is 207%.

The molecules are linked into chains parallel to the *b* axis by N ··· O hydrogen bonds (Table 7). These chains are linked in the *ac* plane *via* the chloride ions

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* See Notice to Authors No. 7, in *J.C.S. Perkin II*, 1975, Index issue.

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TABLE 7

Hydrogen-bond distances (Å) and angles (°), with estimated standard deviations in parentheses

Donor–Acceptor	Distance		Angle
N(3) $\cdots$ O(2$^{\mathrm{I}}$)	2.803(5)	C(4)–N(3) $\cdots$ O(2)	113.1(3)
N(1) $\cdots$ Cl(1$^{\mathrm{II}}$)	3.099(3)	C(2)–N(1) $\cdots$ Cl(1)	126.4(2)
O(1) $\cdots$ Cl(1$^{\mathrm{III}}$)	2.994(3)	C(7)–O(1) $\cdots$ Cl(1)	115.2(2)

Roman numerals as superscripts denote the following transformations relative to the reference molecule at x,y,z: I $-x,\frac{1}{2}+y,\frac{1}{2}-z$ II $x,-1+y,z$ III $-\frac{1}{2}+x,\frac{1}{2}-y,1-z$

TABLE 8

Close contacts involving the chloride ion

(*a*) Distances (Å)

Cl $\cdots$ C		Cl $\cdots$ H	
Cl(1) $\cdots$ C(2$^{\mathrm{II}}$)	3.441	Cl(1) $\cdots$ H(2$^{\mathrm{IV}}$)	2.47
Cl(1) $\cdots$ C(5$^{\mathrm{III}}$)	3.642	Cl(1) $\cdots$ H(4$^{\mathrm{V}}$)	2.64

(*b*) Angles (°)

Cl $\cdots$ H–C	
Cl(1) $\cdots$ H(2)–C(2)	159
Cl(1) $\cdots$ H(4)–C(5)	166

Roman numerals as superscripts denote the operators relative to the reference molecule at x,y,z: IV $\frac{1}{2}-x,-y,\frac{1}{2}+z$ V $\frac{1}{2}-x,-y,-\frac{1}{2}+z$

through Cl $\cdots$ N and Cl $\cdots$ O hydrogen bonds. The chloride ion is also involved in close contacts with C(2) and C(5) of the imidazole ring whereby the C $\cdots$ Cl distances (3.441 and 3.642 Å) are close to those required for C–H $\cdots$ Cl hydrogen-bond formation.[12] Details are given in Table 8.

The acetic acid side-chain is twisted about the C(4)–C(6) bond away from the N(1) side of the imidazole ring, the N(1)–C(5)–C(4)–C(6) torsion angle [13] being −102° (Table 5). This increases the intramolecular N(1) $\cdots$ O(1) distance (Table 9), to a value close to that considered essential for the GABA pharmacophor.[14] The angle between the plane of the imidazole ring and that containing C(7), O(1), and O(2), defining the orientation of the positively charged ring with respect to the carboxylate group, is 73°.

TABLE 9

Intramolecular N $\cdots$ O distances (Å), with estimated standard deviations in parentheses

N(3) $\cdots$ O(1)	4.493(4)
N(3) $\cdots$ O(2)	3.210(4)
N(1) $\cdots$ O(1)	5.714(4)
N(1) $\cdots$ O(2)	4.402(4)

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